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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/991,053	11/21/2001	Richard A. Shimkets	15966-540 CON-S10	3752

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 01/29/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/991,053	SHIMKETS, RICHARD A.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2001*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. The Preliminary Amendment filed on May 23, 2002 has been entered.

Specification

2. The specification is objected to because of the following informalities:

The specification is objected to because on page 1, the continuity data needs to be updated as application number 09/520,781 is now patent number 6,689,866. The specification is also objected to because on page 1 a period is missing where it is disclosed that "...polypeptide chain A signal sequence targets proteins to an intracellular organelle...", see line 19. On page 13 of the specification it is stated that " This sequence between residues 215 to 2173 defines an ORF encoding a protein (SEQ ID NO:10)..." . Note that instead of "residues" it should state "nucleotides".

Correction is required.

Oath/Declaration

3. It is noted that applicant submitted an Oath/Declaration on November 21, 2001, however, the signature page bearing applicant's signature is missing from the application. Resubmission is requested.

Information Disclosure Statement

4. The information disclosure statement filed on 11/21/01 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP 609 because there are items listed on the information disclosure statement that are missing from the application. It has been placed in the application

file, but the information referred to therein has not been considered as to the merits. A line has been drawn through all items on the information disclosure statement.

Basis For NonStatutory Double Patenting

5. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

6. Claims 1-17 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-12, 14 and 19 of copending Application No. 09/957,187. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the claims are directed to a nucleic acid which is identical encoding the same polypeptide and the complement, variant or fragment thereof. The claims in both applications are also directed to vector, host cell, method of producing the polypeptide and a pharmaceutical composition. The copending application recites several other nucleic acid and polypeptide sequences besides SEQ ID NO: 9 and 10 recited in the instant application, thus a different scope. However, the disclosure in the copending application makes obvious the claimed invention in the instant application. Although the scope of the claims herein differs, the two sets of claims are directed to similar inventions since the language in the claim is similar. Thus, the instant application claim is an obvious variation of the copending application claim.

Claim Rejections - 35 USC § 112

7. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid sequence (SEQ ID NO:9) that encodes a polypeptide of SEQ ID NO:10, does not reasonably provide enablement for a nucleotide sequence encoding a protein mutant or variant thereof having no specified activity or sequences that hybridizes under stringent conditions with no defined conditions or fragments of the nucleic acid encoding said polypeptide (claim 1). The claims broadly recites "the nucleic acid sequence which is SEQ ID NO:9, its complement, or a mutant or variant thereof and "a polypeptide of SEQ ID NO:10 or its complement, or a mutant or variant thereof", see claims 3, 6 and 12. In addition, the claims broadly recite fragments of the claimed polypeptide with no recitation of

functional language and an oligonucleotide that hybridizes to the claimed nucleic acid sequence or portion thereof without defining the specific conditions (see claims 1 and 7-9).

In re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) is a statute that lists many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors include but are not limited to: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

I. Quantity of Experimentation Necessary:

The specification on page 2 states that the invention includes an isolated SECX nucleic acid molecule which includes a nucleotide sequence encoding a polypeptide and a naturally occurring polypeptide variant of a SECX polypeptide, wherein the polypeptide is encoded by a nucleic acid molecule which hybridizes under stringent condtions to a nucleic acid molecule consisting of a SECX nucleic acid molecule. The claims have no functional limitation and the claimed sequence could hybridize to nucleotide sequences that may not encode the same protein. For example, Jacobs et al. (WO 99/50405, October 7, 1999) teach a nucleic acid that is 98.9% identical to the claimed nucleic acid which would hybridize, however, does not teach the asserted function for the encoded protein. The specification does not exemplify the claimed protein or a mutant or variant in association with a disease or in a bioassay. Additionally, the hybridization conditions were not recited in the claim and it is well known in the prior art that hybridization

conditions can vary. To examine all the sequences that could hybridize to the claimed sequence to determine if a SECX protein is encoded, would require undue experimentation. The specification on pages 14+ states that the sequence of Clone 3352358 (SEQ ID NO:9) is related to the MEGF (multiple epidermal growth factor-like domains)/Slit family and Roundabout. It is stated that the family is believed to play a critical role in a number of extracellular events including cell adhesion and receptor-ligand interactions. However, mere homology to a family of proteins does not automatically endow function. Moreover, based on a homology of 35% as disclosed in the instant specification and the percent homology disclosed by Jacobs et al. (98.8%) it would appear that the claimed protein belongs to a different family than that disclosed. Therefore, at the time the application was filed, would not have taught one skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.

II. Amount of direction or guidance presented:

The specification does not disclose one reasonable method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim. The specification on page 13 states that the protein encoded by the nucleic acid (SEQ ID NO:9) has 35 % of its residues identical to a human slit-1 protein. It is further stated that slit genes encode proteins with a conserved chemorepulsive activity for axons in invertebrates and vertebrates. For example, the binding of Slit to Roundabout, expressed on the cell surface, is implicated in neuronal guidance activity. Therefore, it is stated that the proteins of the invention has diagnostic and therapeutic utility in pathologies related to neural development and in CNS

pathologies, for example, Alzheimer's disease and Parkinsonism. However, the specification does not exemplify the claimed protein or mutants or variants thereof in a therapy.

The claims are also directed to a fragment of the encoding nucleic acid sequence. However, it is well known in the prior art that changes in a nucleotide sequence can have a dramatic affect on the protein product encoded by the sequence. While the degeneracy of the genetic code accommodates some variation in the nucleotide sequence, the extent of variation evident in applicant's claims ("at least 20 nucleotides", see claims 1) go far beyond alternate codons for the same amino acid. For example, Tuddenham et al. (Nucleic Acids Research, vol. 22, no. 17, pages 3511-3533, 1994) discloses an established database of nucleotide substitutions, deletions, insertions and rearrangements in the Factor VIII gene that causes hemophilia A. The database demonstrates the deleterious impact that various point mutations, deletions and insertions have on the function of Factor VIII. Furthermore, the reference demonstrates that a change of only a single nucleotide may result in loss of function in the protein product (see page 3512 of the reference). Additionally, Tuddenham et al. teach that substitution of an amino acid such as alanine, as a result of the changes to the nucleotide sequence, have a significant functional impact on the polypeptide. The changes to the nucleotide sequence described by Tuddenham et al. are limited in comparison to the wide degree of variability postulated in the instant application for SEQ ID NO:9. A skilled artisan would be led to expect that the variation in the polynucleotide sequence would at best code for a polypeptide that has impaired function and at worst be either nonfunctional or an entirely different product from that of the claimed invention.

Furthermore, the specification lacks guidance/direction as to whether a sequence that hybridizes to the claimed nucleic acid molecule will encode an SECX protein as the claims do not recite any functional language or the hybridization condition. Thus, one skilled in the art would not be able to practice the claimed invention commensurate in scope with the claims.

III. Presence or absence of working examples:

The working examples provided do not demonstrate the claimed variants/fragments in association with the claimed invention.

IV. Nature of the Invention:

The nature of the invention is an isolated nucleic acid that encodes a polypeptide which is said to be an SECX polypeptide, said polypeptide is also encoded by a nucleic acid that hybridizes under stringent conditions to another nucleic acid. The claimed invention is also directed to variants/fragments of the claimed sequence. However, the specification does not provide sufficient guidance/direction to enable the full scope of the claimed invention as no special features/characteristics of the claimed variants/fragments, such as size, length or biological activity is described or demonstrated in the present specification.

V. State of the prior art and Relative skill of those in the art:

The prior art provides general teaching, however, specific not general teaching is what is required, thus a high level of skill was required at the time the application was filed.

VI. Predictability or unpredictability of the art:

Since very little is known in the prior art about the nature of the invention renders the art unpredictable. The specification should then give more details as to how to make and use the invention in order to be enabling. Moreover, as the specification states that portions of the nucleic acid sequence and a sequence that hybridizes to the claimed nucleotide sequence can encode the claimed protein the specification and claims encompass a genus that is highly variable.

VII. Breadth of the claims:

The breadth of the claims are very broad and encompass an unspecified amount of variants/fragments which are not adequately described or demonstrated in the specification.

Thus, the specification contemplates but does not exemplify any functional variants/fragments of the nucleic acid and the encoded protein. Furthermore, there is no demonstration of the claimed protein in a therapy or medicament or assay. No description of the variants/fragments are provided. Furthermore, the claims encompass an unspecified amount of variants/fragments and numerous sequences could hybridize to the claimed nucleotide sequence which may not encode the protein as claimed. In view of the foregoing, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention.

8. Claims 1-17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. The present invention is directed to an isolated nucleic acid that encodes a polypeptide set forth in SEQ ID NO: 10 and variants thereof, and the invention is also directed to nucleic acid sequence at least 90% identical to the nucleic acid sequence encoding said protein. Page 2 of the specification describe the protein as being SECX proteins and indicate that SECX bears a similar function to that of the protein family called MEGF/Slit/Roundabout whose function is speculated to be related to cell adhesion and receptor-ligand interaction activity. However, the assertion that the disclosed SECX has biological activities similar to known MEGF/Slit/Roundabout cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the

specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Therefore, based on the discussions above concerning the specific examples of structurally similar proteins that have different functions, along with the art's recognition that one cannot rely upon structural similarity alone to determine functionality, the specification fails to teach the skilled artisan how to use the claimed nucleotides to make biologically active SECX

without resorting to undue experimentation to determine what the specific biological activities of the SECX are.

The claims recite a nucleic acid sequence at least 90% identical to the nucleic acid sequence the encodes the polypeptide. The claims are also directed to a variant thereof and do not recite a functional limitation to indicate that the function as claimed for the protein is retained. The specification and claims provide no measurable end point to allow one of skill in the art to be able to determine if a polynucleotide that is in possession of another, and having at least 90% identity to SEQ ID NO:9, for example, falls within the description of the polynucleotides as claimed. For example, if another were in possession of a polynucleotide encoding a polypeptide having at least 90% identity to SEQ ID NO: 9, and this polynucleotide encodes a polypeptide having extraordinary activity, such as three times more ability to modulate extracellular events (see page 14 of the instant specification) than that encoded polypeptide disclosed in the instant specification, then this polynucleotide in the possession of another is not described in the instant specification and would not be considered to fall within the limitations of the claims, regardless of the 90% identity limitation. The specification does not describe polynucleotides encoding polypeptides having at least 90% identity to SEQ ID NO:9 and do not modulate extracellular events, for example. The claims must recite a specific, measurable activity such that one can recognize a polynucleotide as that claimed, or a fragment thereof. Therefore, absent adequate written description with regard to a polynucleotide that encodes a polypeptide having at least (90% identity to SEQ ID NO:9, one of skill in the art would have to engage in undue experimentation to determine if the fragment retained the function as asserted in the instant specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 1-17 are rejected under 35 U.S.C. 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is vague and indefinite because the claim recites a fragment of the nucleic acid sequence of (a), (b) or (c) above wherein the fragment comprises at least 20 nucleotides, however, it is unclear if that sequence would encode the polypeptide of (a). The dependent claims hereto are also included.

Claim 3 and 4 are indefinite as a sequence that is complementary, a mutant or variant to items (a) through (d) of claim 1 may not encode the same protein.

Claim 7 is indefinite since the claim does not recite the specific hybridization conditions considered to be "stringent conditions". Note that sequences identified by hybridization would not predictably have the same structural and functional characteristics as the disclosed species because there is no way to determine what variations would be tolerated. It is noted that a discussion is provided in the specification, however, the limitations of the specification cannot be read into the claim. The dependent claims hereto are also included.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claim 1 is rejected under 35 U.S.C. 102 (b) as being anticipated by Ashkenazi et al. (Issued Patents Database_NA, alignment, June 16, 1997).

Ashkenazi et al. teach a nucleic acid sequence that is 92.8% identical to the nucleic acid said to encode SEQ ID NO: 10 in the instant application (see the alignments).

Conclusion

11. No claims are presently allowable.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Hope A. Robinson whose telephone number is (571) 272-0957. The Examiner can normally be reached on Monday - Friday from 9:00 A.M. to 6:30 P.M. (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor Christopher S.F. Low, can be reached at (571) 272-0951.

Any inquiries of a general nature relating to this application should be directed to the Group Receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission. The official fax phone number for Technology Center 1600 is (703) 308-2742. Please affix the Examiner's name on a cover sheet attached to your communication should you choose to fax your response. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG (November 15, 1989).

Hope A. Robinson, MS

Patent Examiner

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER